REMARKS

Claims 1-10 are canceled. Claims 11-23 are currently pending and under consideration. Claims 11-22 have been amended. New claims 24 and 25 have been added. These amended and new claims find support throughout the disclosure (e.g., page 7, line 15 - page 8, line 2; page 9, line 5 - page 11, line 14; page 15, lines 21-25).

In response to the Examiner's indefiniteness-based rejection, currently amended claims 11 and 13 address measuring the inhibition or reduction of the differentiation of Thp cells (claim 11) or measuring the increase in IFNγ levels (claim 13) by comparing of the level of Th2 cells or IFNγ in the subject or sample of interest to the respective level in a control subject or sample. These amendments find support throughout the specification (e.g., page 7, lines 23-25, discusses the contacting step as modulating, e.g., increasing or reducing, IFNγ levels or activity in a cell or cell population; page 9, lines 5-13, discusses the use of IL-21 antagonists to change IFNγ levels or activity in a treated cell; and page 9, line 24 through page 10, line 4, discusses the contacting step as modulating one or more of proliferation, survival and/or differentiation of a Thp cell or cell population into a Th2 cell or cell population; regarding "comparing," see also page 16, lines 8-12). These changes (e.g., increases, decreases) in IFNγ levels and Th2 cell number are relative, e.g., the change is measured by identifying an increase in IFNγ levels in a treated (i.e., contacted) cell population relative to the level in a control untreated (i.e., noncontacted) cell population, or by identifying a decrease in the number of Th2 cells in a treated cell population relative to the number of Th2 cells in a control untreated cell population.

Consideration of the amendments and the remarks herein is respectfully requested.

Rejections based on 35 U.S.C. §112, 1st Paragraph

Claims 11-16 and 18-23 stand rejected under 35 U.S.C. §112 as allegedly failing to comply with the written description requirement. The Examiner maintains that these claims encompass antagonists of IL-21 or IL-21R, and such antagonists are not adequately described in the disclosure. The Examiner argues that while the specification discloses the nucleic acid and amino acid sequences for human IL-21 and human IL-21R, this is insufficient to describe the scope of the antagonists recited in claims 11-16 and 18-23. For the following reasons, that rejection is traversed.

A. The Application Describes Anti-IL-21R Antibodies and Antigen Binding Fragments Thereof.

The Examiner maintains that Applicants have failed to disclose a method of using an anti-IL-21 receptor antibody. (Office Action, dated July 29, 2005, at page 4). Moreover, it is the Examiner's position that because "anti-receptor antibodies can act both as agonists and as antagonists, depending on what conformational changes the antibody induces on the receptor," the antibodies useful in Applicants methods must be "raised against the appropriate epitopes, in order to effectively interfere [with] the ligand/receptor interaction." (Id).

The purpose of the §112 written description requirement is to ensure that an applicant possesses the claimed invention at the time of filing *See Enzo Biochem, Inc. v.*

Gen-Probe, Inc., 323 F.3d 956 (Fed. Cir. 2002). For chemical compounds such as genes or proteins, an applicant must disclose sufficient identifying characteristics so one of skill can "visualize or recognize the identity" of the invention. *Regents of the University of California v. Eli Lilly, Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). For a generic claim, the specification must describe "species sufficient to constitute the genera." *Enzo*, 323 F.3d at 967.

Applicants submit that the specification adequately describes the anti-IL-21R antibody genus useful in the claimed invention. The Federal Circuit has held that disclosing the sequence of a protein is a sufficient written description for claiming antibodies to the disclosed protein. *See Noelle v. Lederman*, 355 F.3d 1344, 1349-50 (Fed. Cir. 2004). Applicants disclose the sequence of human IL-21R and human IL-21, and provide additional information describing the antibodies useful in the methods of claims 11 and 13. For example, claims 11 and 13 recite that the molecules used to either inhibit differentiation of a Thp cell (claim 11) or to increase interferon gamma levels (claim 13) are *antagonists* of IL-21 or the IL-21R. Thus, although certain "anti-receptor antibodies can act as agonists and antagonists, depending on what conformational changes the antibody induces on the receptor" as stated by the Examiner on page 4 of the Office Action, agonist antibodies or antibody fragments are not contemplated as useful in the presently claimed methods. Additionally, Applicants indicate areas of the IL-21R useful as antigens to produce antagonist antibodies. For example, in the instant application, Applicants state that antigenic fragments of the IL-21R useful for raising antagonist antibodies include "at least 7 residues of the amino acid sequence of the amino terminal region [of the IL-21R] (page 22, line 30 - page 23, line 2). Further, in the instant application, Applicants indicate

that hydrophobic epitopes of the IL-21R may be used as antigenic peptides to produce antibodies useful in the claimed methods, and that one might use hydrophobicity analysis programs to generate hydropathy plots useful to identify such epitopes (page 23, lines 2-18). Moreover, the specification identifies PCT Application WO 99/53049, which is directed to methods of producing antibodies against *functionally-relevant* epitopes of a desired protein (page 29, line 29 - page 30, line 2). This application is incorporated by reference at page 5, lines 16-17, of the specification. Therefore, there is ample description in the instant specification of clinically useful antagonist anti-IL-21R antibodies, and Applicants respectfully submit that the disclosure fully describes antagonist anti-IL-21R antibodies used in the claimed methods.

B. The Knowledge of One Skilled in the Relevant Art Provides Anti-IL-21R Antibodies and Antigen Binding Fragments Thereof.

Applicants also respectfully submit that one of ordinary skill in the art would recognize that Applicants were in possession of antibodies useful in the claimed methods. For a chemical compound, an applicant must disclose sufficient identifying characteristics so one of skill can "visualize or recognize the identity" of the invention. *Regents of the University of California,* 119 F.3d at 1568 (Fed. Cir. 1997). However, a specification "need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

At the time of filing, one skilled in the art would recognize, based on the disclosed IL-21R sequence and the knowledge in the art regarding cytokine receptor-ligand interactions, that alignment of the IL-21R sequence with other interleukin receptors would

indicate regions of the IL-21R responsible for ligand binding. Numerous references available at the time of filing discuss that the N-terminus of hematopoietic receptors (and specific domains and residues within the N-terminus of these receptors) are critical for ligand binding and hence receptor signaling. *(See, e.g.,* Woodcock et al. (1994) EMBO J. 13:5176-85; Mulhern et al. (2000) J. Mol. Biol. 297:989-1001; Schimmenti et al. (1995) Exp. Hematol. 23:1341-46; LaRosa et al. (1992) J. Biol. Chem. 267:25402-06; Imler et al. (1992) EMBO J. 11:2047-53; Bazan (1990) Proc. Natl. Acad. Sci. USA 87:6934-38). Gapped BLAST analysis indicates that the human IL-21R disclosed in the current application has 28% identity and 46% homology to the human IL-2 receptor, and that the two receptors score 74.3 bits with a highly significant E value of $6x10^{-13}$. In light of such structural similarity, one skilled in the art could identify functional ligand-binding epitopes useful for producing antagonist antibodies by aligning the IL-21R with the IL-2R. For example, upon reviewing the teachings of Imler et al., *supra*, one skilled in the art would recognize that residues 138 to 153 of the human IL-21R, which correspond approximately to residues 152 to 164 of the human IL-2R, could be used to produce an antagonist anti-IL-21R antibody. Thus, Applicants respectfully submit that one skilled in the art would recognize that Applicants possessed antagonist anti-IL-21R antibodies useful in the claimed methods.

C. The Application and the Knowledge of One Skilled in the Relevant Art Provides Fragments of IL-21R and Fragments with at least 85% Identity to an Extracellular Domain of the IL-21R.

The MPEP §2163 states that addressing the written description requirement of 35 U.S.C. §112 requires the analysis of several factors.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the methods of making the claimed invention. *See Enzo,* 323 F.3d at 964 (Fed. Cir. 2002) (citing *Regents of the University of California*, 119 F.3d at 1566 (Fed. Cir. 1997)).

Applicants respectfully submit that they have adequately described antagonist IL-21R fragments and soluble receptor fragments with at least 85% identity to an extracellular portion of the IL-21R by disclosing the sequence of the IL-21R, identifying the extracellular domain of the IL-21R, disclosing physical properties of antagonist IL-21R fragments, identifying functional characteristics of such fragments, and describing methods of making such fragments. For these reasons, Applicants submit that the application disclosure, coupled with the skill and knowledge in the relevant art at the time of filing, satisfies the written description requirement of §112.

Applicants disclose the full length sequence of the human IL-21 and IL-21R (pages 16-18), and note the public disclosure of the mouse IL-21R sequence (see page 16, line 21, citing Ozaki et al. (2000) Proc. Natl. Acad. Sci. USA 97:11439-44). The specification states that the IL-21R extracellular domain consists of about amino acids 20-235 (page 4, lines 13-15). The specification further discusses an IL-21R fragment as a fragment containing "an IL-21 binding domain" (page 9, lines 19-20). The ability of a useful fragment to interact with IL-21 is also reflected in originally filed (and currently amended) claim 16, which states that the fragment is "capable of binding IL-21" (page 49, lines 12-14). Thus, soluble IL-21R fragments useful in the claimed invention consist of

regions of the extracellular domain of the IL-21R that are capable of binding an IL-21 ligand.

The specification discusses IL-21R sequences with varying degrees of identity to the disclosed human IL-21R sequence. Identity is discussed as preferably ranging from about 50-99% (page 18, lines 19-26). Thus, fragments may vary from the sequence of the IL-21R disclosed, as long as they retain the ability to bind an IL-21 ligand. Variants may include, e.g., those having a mutation in the natural sequence that results in higher affinity to the IL-21 ligand, those having a mutation resulting in increased resistance to proteolysis, those including a signal peptide, and/or those containing a second peptide (such as an Ig fragment) (see, e.g., page 20, lines 5-10; page 21, lines 4-12).

In light of the disclosure, one skilled in the art would instantly recognize that introducing conservative amino acid substitutions in extracellular fragments of the IL-21R would be unlikely to alter ligand binding, and that introducing changes in domains not involved in receptor specificity or folding would also be unlikely to affect ligand binding. At the time of filing, various sources and references identified specific domains and residues within the N-terminus of hematopoietic receptors that were critical for ligand binding and receptor folding. *See, e.g.,* Woodcock et al., *supra*; Mulhern et al., *supra*; Schimmenti et al., *supra*; LaRosa et al., *supra*; Imler et al., *supra*; Bazan, *supra*. In light of the structural similarity of the IL-21R to other hematopoietic receptors (e.g., IL-2, IL-9, etc.), one skilled in the art could identify ligand-binding domains and residues important within these domains that should be included in a useful receptor fragment. For example, upon reading the teachings of Imler et al., *supra*, one skilled in the art would recognize that residues 138 to 153 of the human IL-21R, which correspond to residues 152 to 164 of the

human IL-2R, appear to be relevant in ligand binding. Upon reading the teachings of Bazan et al., *supra*, one skilled in the art would recognize that residues directly N-terminal to the conserved proline pair, which is located at amino acid residues 122-123 of human IL-21R, might also be involved in ligand binding. Upon reading the teachings of Schimmenti et al., *supra,* one skilled in the art would recognize that the conserved WSXWS motif is also important for ligand binding. Upon reading the teachings of Ozaki et al., *supra*, one skilled in the art could align the human and mouse IL-21R sequences to identify conserved residues likely to be involved in ligand binding. Thus, Applicants respectfully submit that one skilled in the art would immediately recognize the amino acid residues that should be retained, and those that could be modified, to create a ligand-binding IL-21R fragment.

As explained above, the specification describes a relatively narrow genus of IL-21R fragments. Fragments contemplated as useful in the claims must bind an IL-21 ligand. Fragments must be derived from either an IL-21R, an extracellular fragment of an IL-21R, or must have at least 85% identity to amino acids 20-235 of the human IL-21R. These fragments must either inhibit or reduce the differentiation of Thp cells to Th2 cells (claim 11) or they must increase IFNγ levels (claim 13). Applicants submit that the specification conveys that they were in possession of IL-21R fragments based on disclosure of structure (sequence), function (inhibition or reduction of Thp cell differentiation or increasing IFNγ levels), biological properties (binding IL-21 ligands), chemical properties (indicating where and what type of amino acid changes may be introduced into the disclosed sequence), and the known structure-function correlation of hematopoietic receptors. Thus, Applicants respectfully submit that they have adequately described the

IL-21R fragments useful in the claimed methods, and respectfully request reconsideration and withdrawal of the written description-based rejections of claims 11-16 and 18-23.

Rejections based on 35 U.S.C. §112, 2nd Paragraph

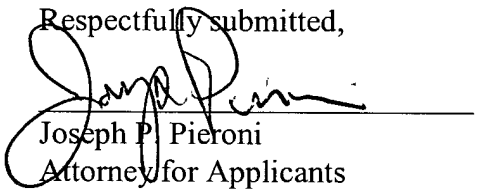
Claims 11-23 stand rejected under 35 U.S.C. §112 as allegedly being indefinite. The Examiner has stated that claims 1 and 16 (Applicants believe the Examiner was referring to claims 11 and 13) do not recite any positive steps, e.g., how inhibition of differentiation of Th precursor cells is measured. Accordingly, Applicants have amended independent claims 11 and 13 to address measuring the inhibition or reduction of the differentiation of Thp cells (claim 11) or measuring the increase in IFNγ levels (claim 13) by comparing of the level of Th2 cells or IFNγ in the subject or sample of interest to the respective level in a control subject or sample. Accordingly, Applicants respectfully request reconsideration and withdrawal of the indefiniteness-based rejections of claims 11-23.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. §112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



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